ANALYSIS OF HEART RATE AND BLOOD PRESSURE VARIABILITY IN PREGNANCY

New Method for the Prediction of Preeclampsia

H. Malberg
Karlsruhe Research Center, Institute for Applied Computer Science, Herrmann-von-Helmholtz-Platz 1 76344 Eggenstein-Leopoldshafen, Germany

R. Bauernschmitt
Clinic for Cardiovascular Surgery, German Heart Center Munich, Germany

T. Walther
Department of Cardiology, Charité, Campus Benjamin Franklin (CBF), Berlin, Germany

A. Voss
Department of Medical Engineering, University of Applied Sciences, Jena, Germany

Renaldo Faber, Holger Stepan
Department of Obstetrics and Gynecology, University of Leipzig, Germany

N. Wessel
Department of Physics, University of Potsdam, Germany

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Abstract: Pre-eclampsia is a serious disorder with high morbidity and mortality occurring during pregnancy; 3%–5% of all pregnant women are affected. Although most pre-eclamptic patients show pathological uterine perfusion in the second trimester, this parameter has a positive predictive accuracy of only 30%, which makes it unsuitable for early, reliable prediction. The study is based on the hypothesis that alterations in cardiovascular regulatory behavior can be used to predict PE. Ninety-six pregnant women in whom Doppler investigation detected perfusion disorders of the uterine arteries were included in the study. Twentyfour of these pregnant women developed PE after the 30th week of gestation. During pregnancy, additional several non-invasive continuous blood pressure recordings were made over 30 min under resting conditions by means of a finger cuff. In the period between the 18th and 26th weeks of pregnancy, three special variability and baroreflex parameters were able to predict PE several weeks before clinical manifestation. Discriminant function analysis of these parameters was able to predict PE with a sensitivity and specificity of 87.5% and a positive predictive value of 70%. The combined clinical assessment of uterine perfusion and cardiovascular variability demonstrates the best current prediction several weeks before clinical manifestation of PE.

1 INTRODUCTION

Pre-eclampsia (PE) is a serious pregnancy-specific disorder. It is characterized by sudden hypertension >140/90 mm Hg and a proteinuria (>300 mg in 24 hours). The manifestation of PE is the main cause of maternal and neonatal morbidity and mortality; it occurs in 3-5 % of all pregnancies.

Although the etiology and pathogenetic factors of the disease are largely unknown, early risk assessment by Doppler sonography has become an established procedure. However, the positive predictive accuracy (PPA) of Doppler sonography is limited to 30 %, as pregnant women with disturbed uterine perfusion may develop a PE, a pregnancy-induced hypertension (PIH), or a neonatal intrauterine growth retardation (IUGR) (Chien, 2000).

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Earlier studies were unable to find either independent markers in the maternal plasma or physiological parameters easy to measure and, in this way, improve the screening efficacy of Doppler sonography (Benedetto, 1998).

Analyses of heart rate variability (HRV), systolic (SBPV) and diastolic blood pressure variability (DBPV) and baroreflex (BR) sensitivity (BRS) were able to demonstrate their high diagnostic and prognostic powers in various studies characterizing autonomous cardiovascular regulation in various diseases (La Rovere, 2001). Various studies demonstrated the suitability of these methods in hypertensive disorders of pregnancy, such as chronic hypertension (Walther, 2005), gestational hypertension (Hermida, 1998), and in PE (Faber, 2004). However, these diseases were clinically manifest already at the time of examination.

In contrast to those other studies, this study employs the approach of looking for characteristic alterations in cardiovascular regulation before the sudden rise of blood pressure. The study is based on the hypothesis that alterations in cardiovascular regulatory behavior can be used to predict PE. Conventional clinical prediction, i.e. Doppler sonography, has to be taken into account. Earlier findings have shown that the sole use of variability analysis in the 18th – 22nd weeks of gestation (WOG) was able to attain a PPA of 50 % (Walther, 2006). In addition, a combined study of variability and uterine perfusion achieved a PPA of 71.6 %, which may be considered the best finding for a non-invasive risk marker of PE at this point in time. In the study outlined below, findings are to be validated in an extended group of patients over a longer period of examination between the 18th and the 26th weeks of gestation.

2 PATIENTS

96 patients with abnormal uterine perfusion (AUP) were included in the study. All pregnant women underwent Doppler sonography in the 2nd trimester of pregnancy (median 22nd week of gestation, WOG, range 18 – 26 weeks) at the Department of Obstetrics and Gynecology of the University of Leipzig. 24 of these pregnant women developed PE after the 30th week of gestation. Approval by the local ethics committee and the informed consent of all subjects were obtained. All pregnancies were singleton. At the time of examination, the women were healthy, normotensive, without clinical signs of cervical incompetence, and on no medication.

Clinically, the development of pregnancy was subdivided in accordance with PE, pregnancy-induced hypertension (PIH), intrauterine growth retardation (IUGR), or pregnancy without any further complications. PE was classified in line with the guidelines of the International Society for the Study of Hypertension in Pregnancy. PIH was described by the rise of several blood pressure levels to more than 140 mm Hg in the systole and more than 90 mm Hg in the diastole within four hours. Significant proteinuria is characterized by an excretion of more than 300 mg of total protein in 24 hours. Where these data were not available, proteinuria was detected by dipstick on two consecutive occasions within four hours. Intrauterine growth retardation was defined by the birth weight being below the 10th percentile of a reference group.

3 METHODS

Doppler examination of the uterine arteries was carried out with a LOGIQ 9 ultrasound machine (GE, Solingen, Germany) with a 5 MHz convex transducer by the same sonographer. Uterine perfusion was classified as pathological when there was bilateral notching or a mean pulsatility index (PI) of both arteries above 1.45. Immediately after the Doppler examination, continuous blood pressure monitoring was conducted non-invasively via finger cuff (100 Hz, Portapres device mod. 2, BMI-TNO, Amsterdam, The Netherlands). The measurements were performed under standardized resting conditions between 8 a.m. and 12 noon. The continuous blood pressure curves were used to extract the time series of beat-to-beat intervals, systolic and diastolic blood pressures.

3.1 Preprocessing

The main objective of the analysis of heart rate and blood pressure is to investigate the cardiovascular system during normal sinus rhythm. Therefore, it is necessary to exclude not only artifacts (e.g. double recognition, i.e. R-peak and T-wave recognized as two beats) but also beats not coming from the sinus node of the heart, so called ventricular premature complexes (VPC). VPCs are not directly controlled by the autonomous nervous system. Practically, this exclusion means filtering of the time series. The original time series are denoted RR-series (derived from the RR-intervals) and the filtered time series, NN-series (normal-to-normal beat interval, NNI). VPCs in the tachogram are usually characterized by

regular ventricular premature beat and supraventricular premature beat complexes). The 20%-filter (Kleiger, 1987) considers these facts; if the current value of the tachogram differs from its predecessor by more than 20%, the current value and its successor are marked not normal. VPCs with less than 20% difference are not removed from the series and may falsify almost all HRV or BPV parameters. The RR-intervals recognized as not normal are treated in different ways: either they are simply removed from the series or interpolated linearly or spline interpolated (Lippmann, 1994). Interpolating linearly may lead to false decreased variability's, interpolating with splines often fails in time series with many VPCs. In several clinical studies, an adaptive filtering algorithm introduced in (Wessel, 2000) has been proven to exclude premature beats and artifacts. The main advantage of this procedure is the spontaneous adaptation to variability changes in the series, which enables a more reliable removal of artifacts and VPCs. This new filtering algorithm consists of three sub-procedures: (i) the removal of obvious recognition errors, (ii) the adaptive percent filter, and (iii) the adaptive controlling filter. A MATLAB implementation of the preprocessing algorithm is available from <tocsy.agnld.uni-potsdam.de>.

3.2 Heart rate and Blood Pressure Variability

Standard methods of HRV analysis include time and frequency domain parameters; these are linear methods. Time domain parameters are based on simple statistical methods derived from the RR-intervals as well as the differences between them. The mean heart rate is the simplest parameter, but the standard deviation over the whole time series (sdNN) is the most prominent HRV measure for estimating overall HRV. A list of these parameters is given in Table 1. These parameters can be calculated for short (5 minutes) and long (24 hours) term epochs, representing short-term and long-term variability, respectively, or for averaged short-term epochs (e.g. a mean of 288 five-minute intervals a day). The overall HRV estimate, sdNN, and other time domain parameters can be used to predict mortality in the recovery period after myocardial infarction. In one of the first risk studies using these parameters, (Kleiger, 1987) showed that an sdNN<50ms was associated with a 5.3-fold increased mortality when compared to patients with preserved HRV (sdNN>100ms).

Time domain geometric methods (see Table 1) are methods by which the NNIs are converted into special geometric forms quantifying their distribution. Special forms are used to make the approach more insensitive to artifacts and ectopic beats. A disadvantage of these methods is that they require a considerable number of RR-intervals; they are thus not applicable to very short-term time series. A triangular index, HRVi, showing reduced HRV has been associated with both arrhythmic and non-arrhythmic death (Task Force, 1996).

Table 1: Description of time and frequency domain parameters, adopted standards (Task Force, 1996) and additional measures developed by the authors (•). NNI stands for the filtered beat-to-beat intervals (NN-intervals).

Variable	Units	Definition
Time domain statistical methods		
meanNN	ms/mm Hg	Mean NNI and mean BP, respectively
sdNN	ms/mm Hg	Standard deviation of all NNI and BP values, respectively
rmssd	ms/mm Hg	Root mean square of successive NNI/BP differences
•pNNX	%	Percentage of beat-to-beat differences greater than X ms/mm Hg (e.g. X = 3/6/9 ms/mm Hg)
•pNNlX	%	Percentage of beat-to-beat differences lower than X ms/mm Hg (e.g. X = 3/6/9/12 ms/mm Hg)
•Shannon	None	Shannon entropy of the histogram (density distribution of the NNIs/ BP values)
•RenyiX	None	Renyi entropy of the order X of the histogram (e.g. X = 2/4/0.25)
Time domain geometric methods		
HRVi	none	HRV triangular index (see (Task Force, 1996) for details)
TINN	ms	Baseline width of the minimum square difference triangle
Frequency domain methods		
P	$ms^2/mm\ Hg^2$	Total power from 0 − 0.4Hz
VLF	$ms^2/mm\ Hg^2$	Very low frequency band, 0.0033 − 0.04Hz
LF	$ms^2/mm\ Hg^2$	Low-frequency band, 0.04 − 0.15 Hz
HF	$ms^2/mm\ Hg^2$	High-frequency band, 0.15 − 0.4 Hz
LF/HF	None	Quotient of LF and HF
LFn	None	Normalized low-frequency band (LF/(LF+HF))
cross 1/f		Intercept of a log-log-power spectrum
slope 1/f		Slope of a log-log-power spectrum

We introduced a more robust method to quantify the distribution (Voss, 1996) based on information theory, in particular the Shannon and the Renyi entropies of the histogram. We demonstrated the usefulness for risk stratification in a blinded study two years later (Voss, 1998). Frequency domain HRV parameters allow periodic dynamics in the heart rate time series to be analyzed (Akselrod, 1981). There are mainly two different techniques for spectral analysis: methods based on Fast Fourier Transform (FFT) and parametric autoregressive model estimates of wavelet approaches. The results obtained from using different spectral methods should be comparable though (apart from differences in time and frequency resolution). The Task Force on HRV (Task Force, 1996) recommended that power spectral analysis of 5-minute ECG recordings be used to assess autonomic physiology and pharmacology.

Very low, low and high frequencies (see Table 1) can be estimated from such 5-minute ECG recordings. In this study, all frequency domain parameters were calculated from the complete 30-minute recording.The high frequency power reflects the modulation of vagal activity by respiration whereas the low-frequency power represents vagal and sympathetic activities via the baroreflex loop. The low-to-high frequency ratio is used as an index of sympathovagal balance (Malliani, 1991). The suitability of frequency domain parameters for risk stratification of post-infarction patients was proven by Bigger et al. (Bigger, 1992) - a reduction in ultra low and very low frequency power is associated with pathologies.For blood pressure series, all HRV parameters described can be calculated accordingly, only some statistical parameters need to be adapted (e.g. pNN50 makes no sense for BPV - the standard deviation for BP series varies between 5 and 10 mmHg).

3.3 Baroreflex Sensitivity

Analysis of spontaneous baroreflex sensitivity (BRS) is very important for cardiac risk stratification of various cardiovascular diseases (La Rovere, 2001). BRS slope is defined as the instinctive change of NNI related to increasing or decreasing levels of systolic blood pressure and is expressed in [ms/mmHg]. There is evidence showing that a decreased BRS may carry an adverse prognosis in cardiac patients (La Rovere, 1998).

For several years, BRS was determined pharmacologically (phenylephrine, nitro-prusside) (Vanoli, 1994) or mechanically (Cohen, 1981) until, in the 1980s, innovative methods of estimating BRS were developed based on spontaneous heart rate and blood pressure fluctuations (Di Rienzo, 1985).

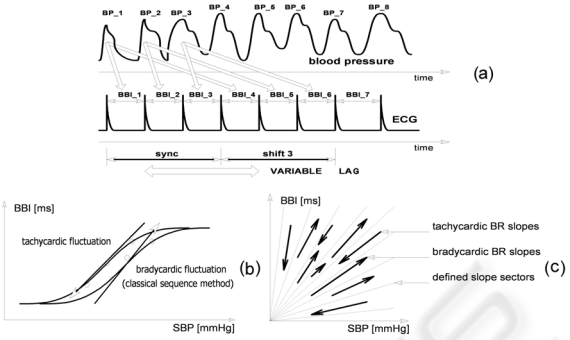

Figure 1: The Dual Sequence Method of estimating spontaneous BRS analyses simultaneous (sync) and delayed responses (shift 3, variable delay) of heart rate to blood pressure increases (a) as well as bradycardic and tachycardic blood pressure fluctuations (classical sequence method (b). Moreover, also the slope sector distribution is quantified (c). These slope sectors also can be defined as overlapping regions.

These methods evaluate arterial baroreflex function in the absence of external stimulations of the cardiovascular system, therefore defined as “spontaneous”. These spontaneous techniques nowadays are the state of the art in research, though not in clinical practice. We introduced the Dual Sequence Method (DSM) (Malberg, 2002) for advanced spontaneous baroreflex sensitivity estimates. This method considers not only bradycardic (blood pressure increase causes RR-interval increase) and tachycardic (blood pressure decrease causes RR-interval decrease) blood pressure fluctuations as introduced in the sequence method (Di Rienzo, 1985) (see Figure 1 (a)), but also defines slope sectors quantifying the BRS slope distribution (see Figure 1 (b)). Earlier studies showed that the heart rate does not simultaneously respond to the blood pressure fluctuation (Manicia, 1985). Therefore, DSM quantifies synchronous as well as delayed heart rate response to the same BP fluctuation (see Figure 1 (c)).

In summary, these are the parameter blocks and ranges calculated by DSM:

(i) the total number of slopes in different sectors within the time series,

(ii) the percentage of slopes relative to the total number of slopes in different sectors,(iii) the numbers of bradycardic and tachycardic slopes,

(iv) the shift operation from the first to the third heart beat triples, a variable lag, and

(v) the average slope of all fluctuations and its standard deviation.

The average BRS slope is defined as the NNI difference related to SBP changes, and is estimated by linear regression.

The parameters, 'P_brady', and, 'P_tachy', characterize the incidence of increasing and decreasing SBP triples with regard to the total number of SBP values. Consequently, these parameters estimate the basic cause of BRS activity. A reduced number of ramps in SBP unavoidably leads to a reduced number of HR responses. The parameters are defined as

*P_brady = (No. of increasing SBP triples/ total No. of SBP triples) * 100%*

*P_tachy = (No. of decreasing SBP triples/ total No. of SBP triples) * 100%*

The percentage of adequate HR responses (BRS events) relative to the numbers of SBP ramps is described by the 'Activation' parameter. It is defined as

*Activation = (No. of BRS events/ No. of SBP ramps) * 100%.*

In contrast to classical BRS methods, DSM defines slope sectors allowing to quantify the BRS slope distribution. Sectors with a range of 2 ms/mm Hg have been proven to act as a suitable partition in patient studies. Then, the percentages of BRS events in different slope sectors relative to the total number of BRS can be estimated. Moreover, the total number of BRS events is normalized to the mean heart rate. For detailed definitions of the DSM parameters, reference is made to the original contribution (Malberg, 2002). These parameters are calculated for bradycardic as well as tachycardic fluctuations, both synchronous or delayed, to analyze a possibly delayed response of the heart rate to the same blood pressure oscillation. This DSM method is used to quantify sequences of length three; longer sequences turned out not to be useful for spontaneous BRS estimates because of their low occurrence.

3.4 Statistics

In this study, the Kruskal-Wallis test was used to determine intergroup differences in clinical parameters. The Mann-Whitney U test was employed to analyze the differences in variability parameters among pregnant women with uterine perfusion disorders developing PE (number = 24) compared to those not developing PE (NoPE, number = 72). The level of significance of the intergroup differences was defined as $p < 0.05$. Due to the explorative character of the study we did not apply the multiple test correction. Stepwise discriminant analysis was employed to determine the best combinations of parameters for separating individual groups.

4 RESULTS

In this study, no pregnant woman with normal uterine perfusion developed hypertensive pregnancy-related disorders. In the period between the 18th and the 26th weeks of gestation, in the abnormal uterine perfusion group, the following differences were found by variability analysis (Tables 2 – 3). In HRV analysis, both the mean and the standard deviation were unchanged, while some frequency domain parameters showed significant differences. Interestingly, all significant parameters point to very low frequencies below 0.04 Hz.

As in the HRV analysis, the mean values and the standard deviation were unchanged also in SBPV and DBPV. On the other hand, especially in DBP, time domain and frequency domain parameters as well as non-linear parameters showed significant differences. The most prominent difference was found to be the 'high frequency' in diastolic blood pressure.

Table 2: HRV analysis in the 18th – 26th weeks of gestation in pregnant women with abnormal Doppler findings developing either PE or NoPE after the 30th week of gestation.

	NoPE	PE	P value
meanNN	759.8±104.4	755.3±113.4	n.s.
sdNN	44.7±16.2	49.0±18.1	n.s.
VLF	10.18±11.45	13.46±11.46	0.013
VLF/P	0.35±0.11	0.44±0.10	0.005
ULF/P	0.21±0.15	0.14±0.08	0.029
cross 1/f	1.79±1.62	3.09±1.48	<0.001
slope 1/f	-0.77±0.56	-0.38±0.51	0.002

Table 3: Analysis of systolic and diastolic blood pressure variability in the 18th – 26th weeks of gestation in pregnant women with abnormal Doppler findings developing either PE or NoPE after the 30th week of gestation.

SBPV	NoPE	PE	P value
meanNN	122.4±16.1	128.6±13.2	n.s.
sdNN	7.81± 2.03	8.36±1.86	n.s.
Rmssd	2.66±0.56	3.02±0.81	n.s.
pNN2	0.27±0.11	0.34±0.13	n.s.
LF	0.14±0.09	0.16±0.07	n.s.
HF	0.03±0.02	0.05±0.03	0.021
WPSUM02	0.46±0.16	0.43±0.11	n.s.
PLVAR2	0.031±0.045	0.014±.0171	n.s.
DBPV	NoPE	PE	P value
meanNN	68.0±11.2	72.9±9.0	n.s.
sdNN	4.15±1.07	4.74±1.43	n.s.
Rmssd	1.89±0.33	2.18±0.59	0.033
pNN2	0.13±0.06	0.20±0.11	0.012
LF	0.05±0.03	0.07±0.04	0.011
HF	0.01±0.01	0.02±0.01	0.002
WPSUM02	0.47±0.14	0.41±0.13	0.049
PLVAR2	0.110±0.083	0.080±0.114	0.004

Also BR regulation as characterized by DSM showed differences in pregnant women developing PE compared to women without PE (Table 4). Analysis reveals that the number of rises in SBP potentially initiating BR increases significantly in PE.

Table 4: Baroreflex analysis by the dual sequence technique in the 18th – 26th weeks of gestation in pregnant women with abnormal Doppler findings developing either PE or NoPE after the 30th week of gestation.

	Bradycardic BR Regulation		
Parameters	**NoPE**	**PE**	**P**
No. of SBP ramps	458.6±94.1	528.1±128.5	0.005
No. of SBP ramps [%]	18.5±2.6	21.1±4.0	<0.001
BR time delay [beats]	1.7±0.4	1.8±0.3	n.s.
No. of slopes between 4-6 ms/mm Hg	35.4±13.6	46.6±22.2	0.019
No. of slopes between 3-5 ms/mm Hg	36.5±15.2	49.1±20.4	0.004
No. of slopes between 5-7 ms/mm Hg	32.2±12.3	41.1±19.2	n.s.
Total No. of BR slopes	173.9±50.0	216.7±77.9	0.009
average BR slope [ms/mm Hg]	13.3±5.6	13.2±5.6	n.s.
BR Activation [%]	38.3±8.7	41.3±10.9	n.s.
	Tachycardic BR Regulation		
Parameters	**NoPE**	**PE**	**P**
No. of SBP ramps	464.9±106.3	527.0±97.3	0.008
No. of SBP ramps [%]	18.8±3.4	21.2±2.7	0.005
BR time delay [beats]	1.5±0.3	1.7±0.5	0.029
No. of slopes between 4-6 ms/mm Hg	41.9±19.3	60.6±20.6	<0.001
No. of slopes between 3-5 ms/mm Hg	47.0±22.7	65.3±24.8	0.003
No. of slopes between 5-7 ms/mm Hg	38.4±17.4	50.2±17.6	0.004
Total No. of BR slopes	200.0±59.1	242.0±64.6	0.005
average BR slope [ms/mm Hg]	12.9±5.6	12.2±6.1	n.s.
BR Activation [%]	43.5±9.4	46.5±11.5	n.s.

Nevertheless, BR per se does not change in its response to activation and mean rise. Also, the total number of BR fluctuations and the number in the low regulation segment (between 3 and 7 ms/mm Hg) is elevated in PE. In the tachycardic range, BR regulation also starts later in the PE group than in the NoPE group.

The application of stepwise discriminant analysis selected the following three parameters as the best parameters predicting PE: HRV: VLF/P, DBP: HF, BR: number of tachycardic slopes between 4-6 ms/mm Hg. A sensitivity and a specificity of 87.5 %, a positive predictive accuracy of 70.0 % were found with a negative predicted accuracy of 95 %. Interestingly, these are the same parameters which had been found in our previous study (Walther, 2006).

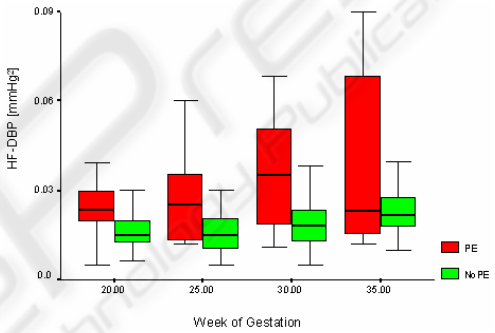

Figure 2: Example of the change in variability measure during pregnancy in the case of PE genesis. The increase in the high-frequency component of diastolic blood pressure is shown.

Figure 2 shows an example of the change over time of variability measure in the course of pregnancy in patients developing PE as against pregnant women without this development.

5 DISCUSSION

Early prediction of PE is one of the most important challenge in obstetrics. Establishing a simple test manageable under clinical conditions is a major challenge. Doppler sonography or combined with humoral or endothelial parameters either attained low sensitivity / sufficient sensitivity or a low positive predictive value and are very costly or even invasive.

Although BRV, BPV, and BRS have been established in cardiology for risk stratification, their use for early detection of hypertensive pregnancy disorders is still very rare. As various cardiovascular dis-

eases can be predicted by a gradual change in cardiovascular regulation, the approach used in this study also was to cover the genesis of PE. This study is aimed at investigating alterations in HRV, BPV and BRS to predict the sudden steep increase of blood pressure which is caused by PE.

With an incidence of 3 – 5 % of all pregnancies in the Western population, pathological uterine perfusion in the second trimester is known as an indirect sign of inadequate trophoblasts. The positive predicted value of this study, however, is only around 30 %. In an earlier study of the variability analysis of PE, the authors were able to show that the use of only the variability parameter was able to raise to 50 % the positive predictive value, which does represent the highest possible PPA, but is not yet sufficient for clinical routine screening. Except for that, the three variability parameters described above attained the highest PPA of any one method of examination which, in addition, is independent of humoral factors and other single clinical parameters.

This study has shown that the combination with Doppler sonography of uterine arteries confirms the highest possible PPA as compared to all published non-invasive trials (Walther, 2006). The PPA of approx. 70% is indicative of the clinical relevance of Doppler examination combined with variability analysis. However, due to the exploratory design of this study, these parameters need to be validated prospectively - especially in connection with humoral factors. Anyway, the same three parameters, which had been found in our previous study (Walther, 2006), were selected in the discriminant analysis. These parameters obtained nearly the same classification results – which is already a first validation.

On the basis of the variability measures determined, the following interpretation could be possible in the course of pregnancy for the genesis of PE in a cardiovascular model (see Figure 3).

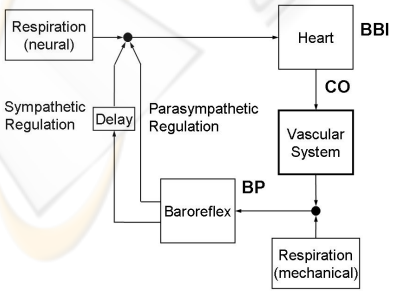

Figure 3: Connections between the heart rate, NNI, the cardiac output, CO, and the blood pressure, BP, in autonomous regulation of the cardiovascular system, modified from [Saul, 1991)

In Figure 3 a simplified model of the cardiovascular circulatory system is presented. Mediated by the electromechanical coupling, the NNIs initiate a cardiac output (CO) of the heart. The resulting blood pressure in the periphery is influenced by this CO and by the vascular system. In the feedback the NNIs are influenced by the BRS via sympathetic and parasympathetic activation. Additionally, the total system is superimposed by mechanical and neuronal influences of the respiration.

Our analyses point to a more vascular disorder as the cause of the cardiovascular alteration. Obviously, the heart plays only a secondary role. Apparently, there is an early pathological modification in vessel behavior measurable already in the Doppler sonogram. However, this parameter obtains a low PPA only. This incipient endothelial dysfunction, which is still very weak in the 18th – 26th weeks of gestation, has no influence on the mean values of diastole, systole, and heart rate. On the other hand, especially the variability of blood pressure seems to change as a consequence of continuing pathological arterial stiffness in so far as the minor fluctuations in blood pressure become more pronounced as a result of the decreasing windkessel function of vessels. This can be represented by the changes in blood pressure variability (see parameters: SBPV: ‘HF’, DBP: ‘Rmssd’, ‘pNN2’, ‘LF’, ‘HF’, ‘WPSUM02’, ‘PLVAR2’, BRS: ‘No. of SBP ramps’, ‘No. of SBP ramps [%]’). The baroreflex reacts more strongly to this change, i.e. it reacts more frequently to these slight, but more frequent blood pressure stimuli (see BR parameters: ‘No. of slopes between 4-6 ms/mm Hg’, ‘No. of slopes between 3-5 ms/mm Hg’, ‘No. of slopes between 5-7 ms/mm Hg’, ‘Total No. of BR slopes’). The baroreflex function (i.e. the intensity of response of the BR) seems to be completely unchanged (see BR parameters: ‘average BR slope’, ‘BR activation’). The changes in BPV and BR are continued in HRV either as a consequence of the counter regulation of the heart rate responding to blood pressure fluctuations, or due to other regulatory influences modulated by respiratory sinus arrhythmia (see HRV parameters: ‘VLF’, ‘VLF/P’, ‘ULF/P’, ‘cross 1/f’, ‘slope 1/f’). Thus, for example, the increase in diastolic high frequency, which is modulated by respiratory sinus arrhythmia, may reflect early pathological arterial stiffness. This leads to the undamped, respiration-induced pulse-wave oscillations detected by our method. This is congruent with the hypothesis that patients later developing PE are characterized by early pathological modifications in vessel behavior. The physiological conclusion could be drawn that variability analysis meas-

ures the consequences to blood pressure, to the interaction between blood pressure and heart rate, and to the heart rate of incipient endothelial dysfunction, which is not thought to be sufficient to predict PE solely on the basis of the Doppler sonogram.

In a previous methodological study the applicability of different BR methods was tested (Vanoli, 1994, Laude, 2004). All described methods estimate only the average BRS slope. The DSM however, is able to obtain additional insights into the cardiovascular regulation. In this study, 'average slope' is not altered, however more sophisticated DSM parameters found high significant differences. So we conclude, that the parameter 'average slope' is not sufficient for PE prediction. The best discrimination had been obtained by the combination of non-linear BR parameters and linear HRV und BPV parameters.

In summary, it can be said that examination of uterine perfusion combined with the characterization of cardiovascular regulation in the second trimester has achieved the most accurate prediction of PE several weeks before its clinical manifestation so far. In this application, the biosignal analysis emphasizes its importance as a non-invasive, cheap and universal diagnostic approach. This opens up potential therapeutic strategies for suppressing pathophysiological symptoms of the disease to further decrease maternal and neonatal morbidity and mortality rates.

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